Histopathological Features of Common Pediatric Brain Tumors

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Introduction

Collectively, central nervous system (CNS) tumors are the most common solid tumors in the pediatric population and are the leading cause of cancer-related death in this age group. These tumors display diversity in their cellular origin, biology, management options, and long-term outcomes. Microscopic examination combined with molecular signatures of these tumors continues to identify and define features specific to CNS tumor subtypes. Intra- or postoperative histological analysis of biopsies and resections thus continues to play an important role in providing a specific diagnosis that helps guide the appropriate subtype-specific management and care for each patient.

In this chapter, we provide a brief overview of the main diagnostic histopathological features of the common pediatric CNS tumors to aid in the appreciation of how brain tumors are subclassified by neuropathologists. Some diagnoses can be made immediately on standard hematoxylin and eosin stains based on classic architectural features alone, while more challenging cases often require ancillary studies including immunohistochemistry, electron microscopy, cytogenetics, and/or molecular studies. For the interested readers, texts dedicated to the neuropathology of brain tumors may be consulted for a more detailed review [1, 2].

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Neuroepithelial Tumors

Astrocytic Tumors

Pilocytic Astrocytoma

Pilocytic astrocytomas (WHO grade I) are the most common group of pediatric gliomas, and typically present in the cerebellum or midline along the hypothalamic/optic pathways [3]. Grossly, pilocytic astrocytomas are well-circumscribed, soft, and often cystic lesions. Microscopic examination of classic pilocytic astrocytomas characteristically shows a biphasic histologic pattern comprised of a compact fibrillary component that neighbors a spongy microcystic element (Fig. 6.1a). The compact component is formed by parallel fascicles of bipolar hair-like (piloid) astrocytic cells with

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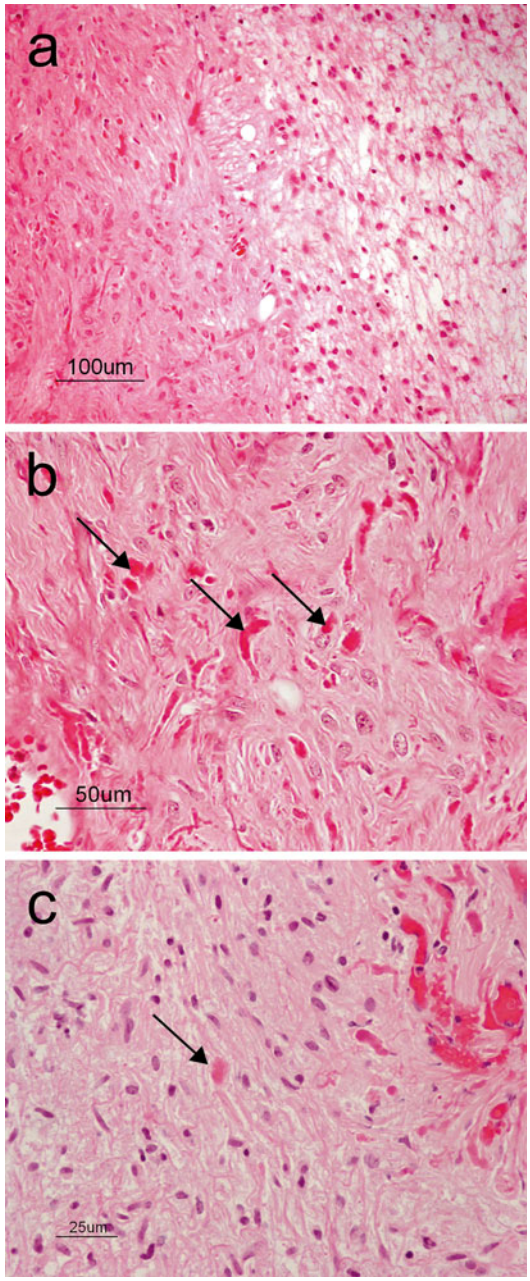

Fig. 6.1 (**a**) Pilocytic astrocytoma showing biphasic architecture, with both a loose, hypocellular pattern (right half) and a compact cellular pattern (left half). H&E, original magnification ×100. (**b**) Rosenthal fibers (*arrows*) scattered within the compact piloid component of a pilocytic astrocytoma. H&E, original magnification ×200. (**c**) Eosinophilic granular body (*arrow*) within a loose area in a pilocytic astrocytoma. H&E, original magnification ×200

bland nuclei and long, narrow cytoplasmic processes in a fibrillary background rich in Rosenthal fibers (Fig. 6.1b, c). These fibers are brightly eosinophilic, proteinaceous, intracytoplasmic, glial fibrillary acidic protein (GFAP)-positive masses that are characteristic of, but not specific for, pilocytic astrocytoma. The less cellular component consists of loose, hypocellular, microcystic areas made up of cells with small round nuclei and fine processes and with scattered cells containing another type of globular, brightly eosinophilic, aggregate known as eosinophilic granular bodies (EGBs) (Fig. 6.1c). Although prognosis is generally good, incomplete resection of the lesion is associated with recurrence of the cystic component [4].

The presence of microscopic foci of brain or subarachnoid space infiltration, occasional mitotic figures, isolated foci of necrosis, or microvascular proliferation does not necessarily indicate malignancy or poor survival [5]. Innocent degenerative changes such as nuclear atypia and pleomorphism associated with smudgy chromatin and nuclear pseudo-inclusions can occur and may lead to misdiagnosis of a malignant glioma. Other degenerative changes that can be seen include the presence of multinucleated giant cells (often referred to as "pennies on a plate"). Malignant transformation is rare and typically results following radiation therapy of this low-grade lesion [5].

Immunohistochemically, pilocytic astrocytomas have a low Ki67/MIB-1 proliferative index of 1–4 % (but sometimes higher) and stain for GFAP. When the location of these tumors limits adequate biopsies, it is often difficult histologically to differentiate them from other low-grade lesions such as diffuse astrocytomas (WHO grade II). Molecular testing in these cases may provide some aid, as the majority (70 %) of cerebellar pilocytic astrocytomas exhibit activation of the RAS/BRAF/MAPK pathway commonly due to BRAF duplication/fusion with the KIAA1549 gene, something less commonly seen in diffuse astrocytomas [6].

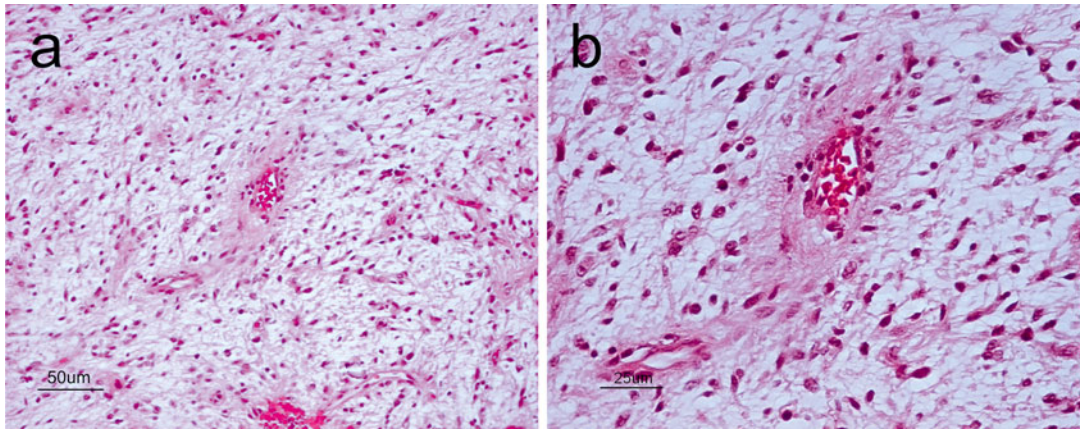

Fig. 6.2 (**a**) Pilomyxoid astrocytoma showing a monophasic architecture in a myxoid background. There is an impression of the angiocentric pattern at this low power that is better seen at higher power. H&E, original magnification ×200. (**b**), Angiocentric pattern of pilomyxoid astrocytoma. H&E, original magnification ×400

A potential diagnostic mimic of pilocytic astrocytoma is nonneoplastic reactive gliosis which can resemble a pilocytic astrocytoma due to increased numbers of astrocytes and the presence of Rosenthal fibers. Such so-called piloid gliosis classically occurs at the rim of a craniopharyngioma or a hemangioma where the surrounding brain tissue creates a dense gliotic background filled with Rosenthal fibers, but can occur around any long-standing or slowly expanding lesion. Biopsies from these areas may be misinterpreted as findings consistent with a pilocytic astrocytoma, underscoring the need for adequate surgical sampling.

Pilomyxoid Astrocytoma

This pediatric tumor entity shares many of the gross and microscopic features of pilocytic astrocytomas. Like pilocytic astrocytomas, these tumors tend to occur in midline structures, with a predominance for the suprasellar/hypothalamic region [7]. Their increased tendency to recur and less favorable prognosis have resulted in designating pilomyxoid astrocytoma as a distinct WHO grade II entity rather than simply as a rare morphologic variant of pilocytic astrocytoma [7].

Grossly, pilomyxoid astrocytomas are well-circumscribed, solid, gelatinous, or cystic lesions that are difficult to distinguish macroscopically from pilocytic astrocytoma. On microscopic examination however, unlike its close relative, pilomyxoid astrocytoma is a monophasic tumor in a predominantly myxoid background matrix (Fig. 6.2a). Embedded within the myxoid matrix are bland bipolar cells that have a tendency to form an angiocentric pattern (Fig. 6.2b). Other histological findings that may help in distinguishing this entity from pilocytic astrocytoma are its lack of protoplasmic cells, Rosenthal fibers or calcifications, and rare eosinophilic granular bodies. Neither immunohistochemistry nor molecular testing has been helpful thus far in distinguishing pilomyxoid from pilocytic astrocytoma.

Angiocentric Glioma

This entity was added to the WHO 2007 classification as a WHO grade I lesion and carries a good prognosis [2, 8]. They are cortically based, typically occurring in the frontoparietal and temporal lobes (including the hippocampal region), and present clinically with seizures. Microscopically, angiocentric gliomas are variably infiltrative and characterized by monomorphous bipolar cells with a prominent angiocentric growth pattern (Fig. 6.3a). They also frequently display subpial palisading. As for most astrocytic neoplasms, GFAP is diffusely positive. There is also an intracytoplasmic dot-like pattern of staining with epithelial membrane antigen (EMA) (Fig. 6.3b).

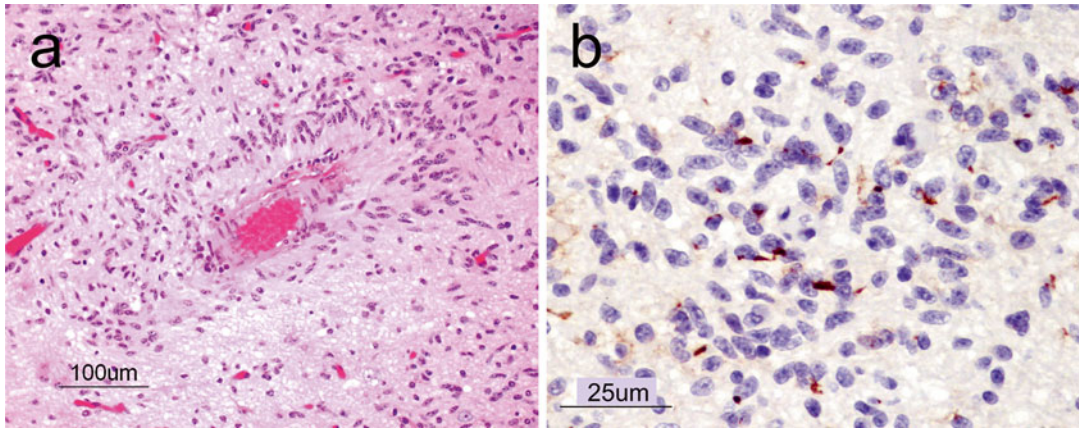

Fig. 6.3 (**a**) Angiocentric glioma showing elongated astrocytic tumor cells organizing around a blood vessel (angiocentric pattern). H&E, original magnification ×100. (**b**), A dot-like staining pattern with epithelial membrane antigen (EMA) immunohistochemistry is a characteristic feature of angiocentric glioma. Original magnification ×400

Diffuse Astrocytoma

Diffuse astrocytomas (WHO grade II) are infiltrating glial tumors that occur throughout the pediatric CNS. Unlike in adults, diffuse astrocytomas in children rarely progress to higher grade lesions. Grossly, this tumor forms an ill-defined and occasionally cystic mass that causes enlargement and distortion of the involved anatomical structures.

Microscopically, diffuse astrocytomas are composed of hypercellular sheets of cells with oval to elongate nuclei within a fibrillar background (Fig. 6.4a). The entrapment of nonneoplastic neurons (Fig. 6.4b) and features such as perineuronal, perivascular, subpial, and subependymal aggregates of neoplastic cells (the so-called secondary structures) are evidence of their infiltrative growth. The presence of atypical nuclei that are angular, hyperchromatic, and mildly pleomorphic can help differentiate these neoplasms from reactive astrocytes. Mitoses, however, are rare or absent. GFAP is the main immunohistochemical stain that highlights the neoplastic astrocytic cells. Neurofilament is helpful for highlighting the infiltrative nature of the tumor cells (Fig. 6.4c).

Morphological variants of diffuse astrocytomas include protoplasmic and gemistocytic variants. The former is a rare hypocellular, mucoid, and microcystic lesion that is predominantly composed of cells with small nuclei, low content of glial filaments, and scant GFAP expression. The gemistocytic variant shows a predominant population of cells with abundant eosinophilic cytoplasm, nuclei that are displaced to the periphery and strong, consistent GFAP expression.

Recently, a study applying whole-genome sequencing to low-grade gliomas found a high rate (53 %) of either intragenic duplication of the tyrosine kinase domain of the FGFR1 or rearrangements of MYB in WHO grade II diffuse gliomas [9]. In a similar analysis of grade II gliomas, 28 % were shown to have partial duplication of the transcription factor MYBL1 [10]. Given the availability of specific therapeutic inhibitors of such pathways, histopathological diagnosis with supplemental molecular analysis of tumors may one day offer more patient-specific treatments and prognostication for these tumors.

Anaplastic Astrocytoma

Anaplastic astrocytomas (WHO grade III) show increased cellularity, nuclear pleomorphism, and hyperchromasia when compared to WHO grade II diffuse astrocytomas. Grossly, it is difficult to differentiate between diffuse astrocytoma WHO grade II and anaplastic astrocytoma.

The presence of mitoses is a key distinguishing feature that favors a diagnosis of anaplastic

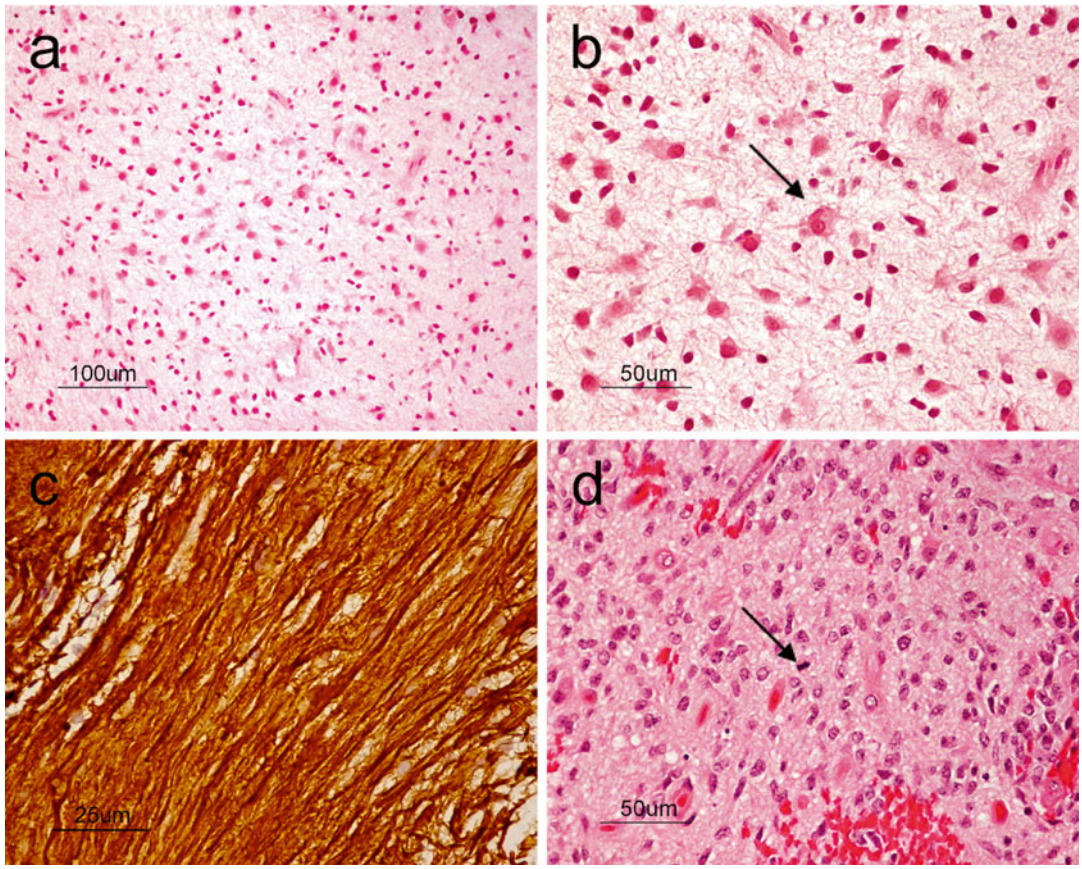

Fig. 6.4 (**a**) At low power, diffuse astrocytoma can be recognized as areas of hypercellularity within the brain. H&E, original magnification ×100. (**b**), On higher power, entrapped neurons (*arrows*) can be seen demonstrating the infiltrative nature of the tumor. H&E, original magnification ×200. (**c**), Neurofilament immunostain highlighting the infiltrative nature of the tumor. H&E, original magnification ×400. (**d**), Anaplastic astrocytoma showing markedly increased cellularity, nuclear pleomorphism, and mitosis (*arrow*). H&E, original magnification ×200

astrocytoma over the lower grade astrocytic neoplasms already discussed (Fig. 6.4d). Though the finding of pyknotic nuclei is still consistent with this category, geographic areas of necrosis or microvascular proliferation are usually indicative of glioblastoma.

Glioblastoma

Glioblastoma (GBM) is a malignant astrocytic tumor (WHO grade IV) that can occur throughout the CNS. It is less common in the pediatric population than in adults. As its former name "glioblastoma multiforme" suggests, the tumor exhibits tremendous phenotypic heterogeneity from one region of the tumor to another. Grossly, it usually shows areas of necrosis, hemorrhage, peritumoral edema as well as occasional pseudocapsule formation, in addition to a yellowish discoloration from myelin breakdown. GBMs also exhibit variable architectural patterns and cellular morphologies at the microscopic level that include multinucleated giant cells, small cells, granular cells, and lipidized cells. In addition to sharing features such as hypercellularity, diffuse infiltration, pleomorphism, and mitoses with anaplastic astrocytoma, GBMs also show either necrosis, typically with pseudopalisading of tumor cells (Fig. 6.5a) or microvascular proliferation (Fig. 6.5b).

Exome sequencing of pediatric supratentorial/hemispheric GBMs has revealed differences in the biology that governs tumorigenesis between

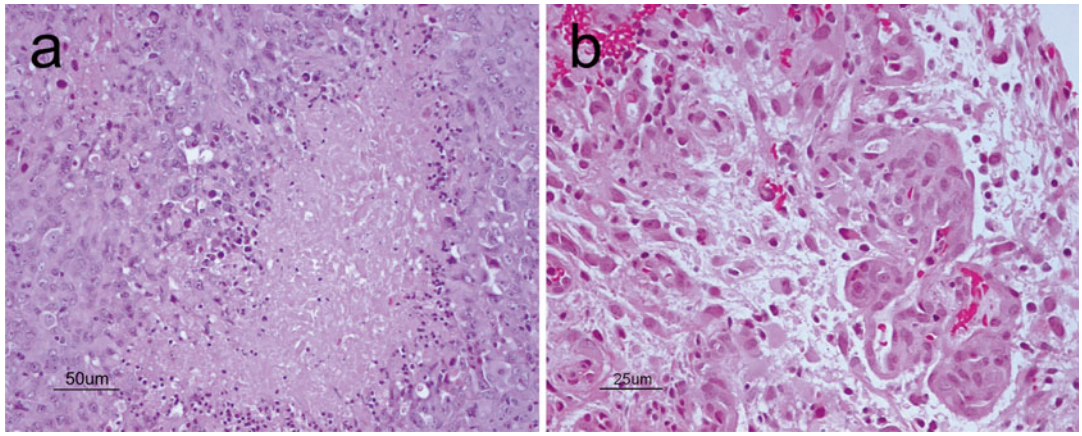

Fig. 6.5 (**a**), Classical palisading of the neoplastic cells around areas of necrosis. H&E, original magnification ×200. (**b**) vascular-endothelial proliferation. H&E, original magnification ×400

pediatric/young adult GBMs and those seen in adults. In the young age group somatic mutations in the H3.3-ATRX-DAXX chromatin remodeling pathway can be found. Mutations in the tumor suppressor *TP53* are found in approximately half of GBMs and 86 % of GBMs with H3.3 or ATRX mutations. Mutations in H3.3 were also highly specific for GBMs when compared to low-grade lesions and thus provide additional tools to help differentiate between the different tumor grades in small biopsies [11]. Although extremely rare in the pediatric population, IDH1 mutations may be encountered in the adolescent age group [12].

Pleomorphic Xanthoastrocytoma

Pleomorphic Xanthoastrocytoma (PXA) is a relatively rare astrocytic, low-grade tumor (WHO grade II) with distinctive morphologic features. It is a supratentorial lesion that classically involves the superficial cortex and leptomeninges of the temporal lobe of children and young adults with medically refractory epilepsy. Grossly, PXAs are discrete lesions with leptomeningeal involvement and may be cystic lesions. Microscopically, as its name suggests, PXAs are composed of highly pleomorphic, fibrillary astrocytes, some of which may show lipidization (Fig. 6.6a). Large, bizarre, multinucleated cells are an additional feature. Reticulin positivity is a characteristic feature (Fig. 6.6b). Eosinophilic granular bodies, perivascular infiltration by lymphocytes, and a solid component within the subarachnoid space are key features that can help with diagnosis. Due to its significant pleomorphism, differentiation of PXA from more malignant astrocytic tumors such as anaplastic astrocytoma or GBM is critical given the difference in prognosis. In fact, even when PXAs show "anaplastic features" (5 or more mitoses per 10 high power fields) or necrosis, the prognosis still remains more favorable than that of high-grade gliomas [13]. The neoplastic cells in PXA are positive for S100 and variably positive for GFAP and CD34 [14]. There may also be focal areas with a neuronal phenotype suggesting a multipotential precursor cell as its cell of origin [15]. Approximately two-thirds of PXAs harbor the V600E BRAF mutation [16].

Embryonal Tumors

Medulloblastoma

Medulloblastoma (WHO grade IV) is the most common malignant pediatric brain tumor. It characteristically occurs in the cerebellum and in the roof of the 4th ventricle, where it forms a well-circumscribed, soft, gray mass presenting as cerebellar dysfunction and obstructive hydrocephalus with cranial nerve findings. It has a tendency to infiltrate the leptomeninges and form spinal "drop metastases" via the CSF.

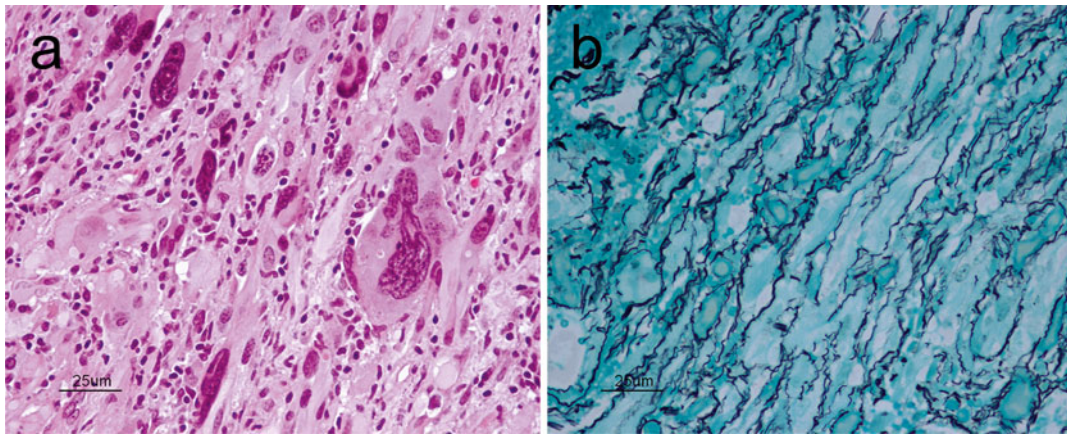

Fig. 6.6 (**a**) PXA showing pleomorphic fibrillary astrocytes, including large bizarre cells. H&E, original magnification ×400. (**b**), PXA typically exhibits an extensive reticulin network. Reticulin, original magnification ×400

Histologically, it is divided into classic medulloblastoma (majority of cases) and less common variants that include desmoplastic/nodular medulloblastoma, medulloblastoma with extensive nodularity, anaplastic medulloblastoma, and large cell medulloblastoma.

As discussed in Chap. 12, medulloblastomas can also be divided into four distinct molecular subgroups with some enrichment for the histological types. Here we will discuss the histologic variants.

The classic medulloblastoma subtype makes up approximately 70 % of all medulloblastomas and forms sheets of small round blue cells (high nucleus-to-cytoplasmic ratio) containing variable numbers of Homer-Wright (neuroblastic) rosettes characterized by a fibrillary core (Fig. 6.7a,b) and rarely differentiating ganglioneuronal elements. Medulloblastomas usually exhibit a high mitotic rate, numerous apoptotic bodies, and small areas of necrosis. The tumor cells show positivity for neuronal immunohistochemical markers such as synaptophysin, NeuN, anti-Hu, and neuron-specific enolase in addition to focal positivity with glial markers like GFAP [17].

Nodular/desmoplastic medulloblastoma is the second most common histopathological variant of medulloblastomas. Grossly, it has a firm consistency and unlike the classic form that tends to occur in the vermis, it arises in the cerebellar hemispheres. Microscopically, pale zones showing neurocytic differentiation and apoptosis are surrounded by more cellular zones that are reticulin-rich and highly proliferative (Fig. 6.7c,d). The differentiated nodules may be highlighted using neuronal markers such as synaptophysin. Nodular/desmoplastic medulloblastomas are associated with Gorlin syndrome and activation of the sonic hedgehog pathway [17].

Medulloblastoma with extensive nodularity is a rare variant, usually seen in infants, with a favorable prognosis. It is qualitatively differentiated from the nodular/desmoplastic type variant by having a predominant lobular architecture with large elongated reticulin-free zones that contain small round neurocytic cells in a fibrillary background. The internodular component of reticulin-rich areas that is commonly seen in desmoplastic medulloblastoma is largely reduced [18].

Anaplastic/large cell medulloblastomas are thought to be more aggressive variants. Anaplastic medulloblastomas show marked nuclear enlargement, nuclear pleomorphism, nuclear molding, high mitotic count, prominent necrosis, and apoptosis (Fig. 6.7e). Large cell medulloblastoma has discohesive, monomorphic large cells with round nuclei, open chromatin, and prominent nucleoli (Fig. 6.7f). The features of "anaplastic" and "large cell" may coexist in the same tumor [2].

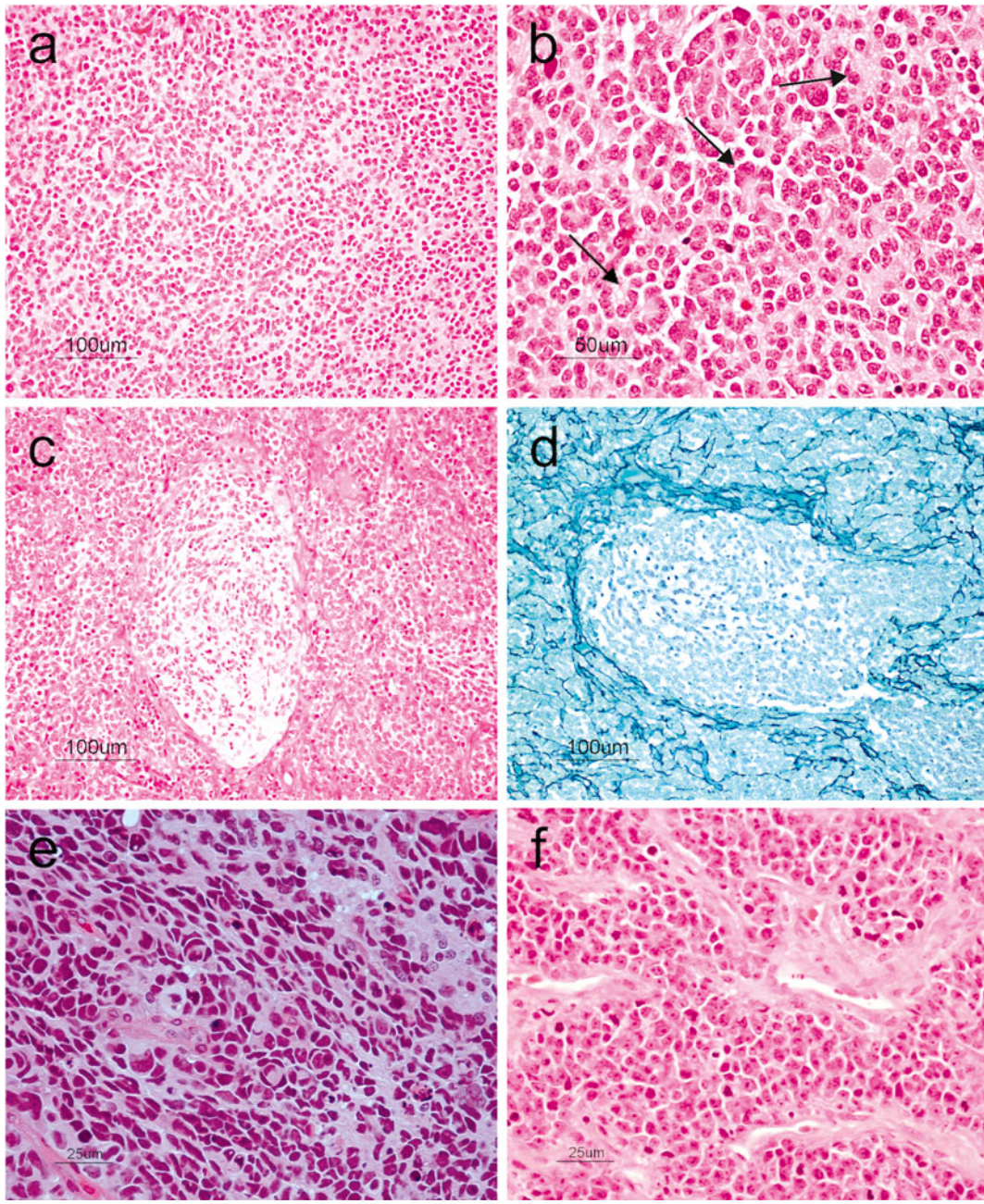

Fig. 6.7 (**a**) Small round blue cells characteristic of medulloblastoma. H&E, original magnification ×100. (**b**) Tumor cells arranged in Homer-Wright rosettes (*arrows*). H&E, original magnification ×200. (**c**), Desmoplastic medulloblastoma showing pale nodular areas in between more cellular internodular regions. H&E, original magnification ×100. (**d**) Reticulin-rich internodular regions in desmoplastic medulloblastoma. Reticulin, original magnification ×100. (**e**) Anaplastic medulloblastoma showing markedly pleomorphic cells, cell molding, and prominent apoptosis. H&E, original magnification ×400. (**f**) Large cell medulloblastoma showing large anaplastic cells with prominent nucleoli and vesicular chromatin. Note the prominent apoptosis. H&E, original magnification ×400

Other variants include medulloblastomas with melanotic or myogenic differentiation that can be highlighted by melanocytic and myogenic markers, respectively. Although histologically distinctive, these variants do not have any known prognostic significance at this time [2].

Even among histologically similar medulloblastomas, genomic approaches have helped further subclassify these tumors into clinical and biologically distinct groups. Four subgroups are currently recognized: WNT, SHH, Group 3, and Group 4. Not only will these groups provide better prognostic information for patients, but these also help stratify tumors into classes driven by distinct molecular pathways, which have the potential to be translated clinically into more patient-specific therapies [19]. These classes are discussed in more detail in Chap. 12.

Supratentorial Primitive Neuroectodermal Tumor

Supratentorial Primitive Neuroectodermal Tumor (sPNETs) (WHO grade IV) are tumors morphologically similar to medulloblastomas but that reside in the cerebral hemispheres rather than the cerebellum of children and adolescents. Compared to medulloblastomas, sPNETs are less frequently encountered and carry a worse prognosis. This tumor is mostly situated deep within the hemisphere. Usually, they are soft and pink-red to purple in color with or without cystic changes or hemorrhages. Microscopically, they resemble medulloblastomas exhibiting sheets of poorly differentiated small round blue cells with hyperchromatic nuclei and a high nucleus-to-cytoplasmic ratio (Fig. 6.8a). Homer-Wright rosettes are found with variable frequency. Areas of necrosis, abundant mitoses, and apoptosis can be seen [2]. Immunohistochemistry may demonstrate areas of divergent differentiation including neuronal, glial or, more rarely, mesenchymal. When large ganglion cells are seen disbursed throughout neuroblastic differentiation, the term ganglioneuroblastoma may be used [2].

Similar and very rare primitive embryonal tumors include those with predominant neural

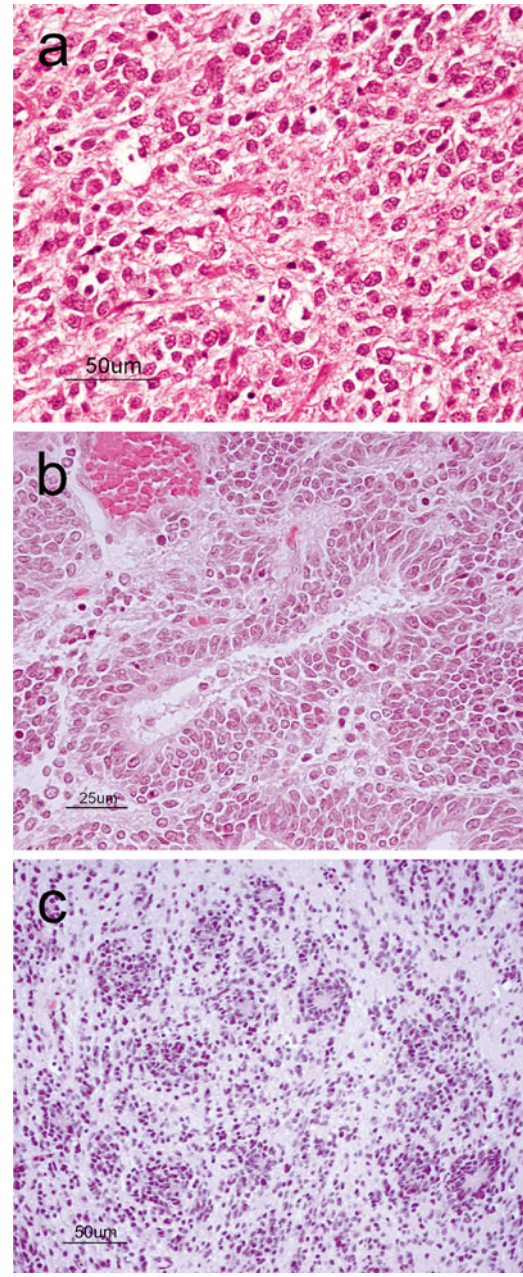

Fig. 6.8 (**a**) sPNET showing a cellular neoplasm with hyperchromatic, anaplastic nuclei, and numerous apoptotic bodies. H&E, original magnification ×200. (**b**) Medulloepithelioma showing the characteristic tubular structures mimicking the primitive neural tube. H&E, original magnification ×400. (**c**) Embryonal tumor with abundant neuropil and true rosettes demonstrating the biphasic architecture with hypercellular regions abutting hypocellular fibrillary regions. H&E, original magnification ×200

tube formation termed medulloepithelioma (Fig. 6.8b). A newly described variant is the so-called "embryonal tumor with abundant neuropil and true rosettes" (Fig. 6.8c) that shows focal areas of hypercellularity, broad bands of neuropil and rosettes with slit-like lumens and has an extremely poor outcome [20]. This tumor is characterized by frequent amplifications at chromosome 19q13 [21].

Genetic analysis of childhood PNET tumors has also been able to further subclassify these tumors into three distinct molecular subgroups with significantly different clinical outcomes based on their expression of LIN28 and OLIG2 [22]. These subgroups are discussed in more detail in Chap. 12.

Atypical Teratoid/Rhabdoid Tumor

Atypical Teratoid/Rhabdoid Tumor (ATRT) is a high-grade (WHO grade IV) tumor that can occur both supra- and infratentorially [2]. It commonly affects children below the age of 3 years and like other embryonal tumors, ATRT creates a soft pink mass with foci of necrosis. Microscopically, this heterogeneous tumor consists of large pale cells, areas of undifferentiated PNET-like small round blue cells, and areas with classic rhabdoid cells with pleomorphic eccentrically placed nuclei with vesicular chromatin and prominent nucleoli that are displaced from the center of the cell by an eosinophilic filamentous inclusion in the cytoplasm (Fig. 6.9a). Mitoses are usually abundant and the MIB-1 proliferative index is typically very high (up to 80 %). Necrotic areas are common, as are apoptotic bodies. Immunohistochemical studies may show tumor cell positivity for vimentin, EMA, smooth muscle actin as well as focally for GFAP, cytokeratin, neurofilament, and synaptophysin. They are typically negative for desmin. Typically, the tumor cells are immuno-negative for INI-1 (Fig. 6.9b) and show 22q11.2 deletions involving the hSNF5/IN1 gene [23]. This feature is diagnostically very useful in distinguishing ATRT from sPNET, choroid plexus carcinoma, and medulloblastoma which it may mimic [2].

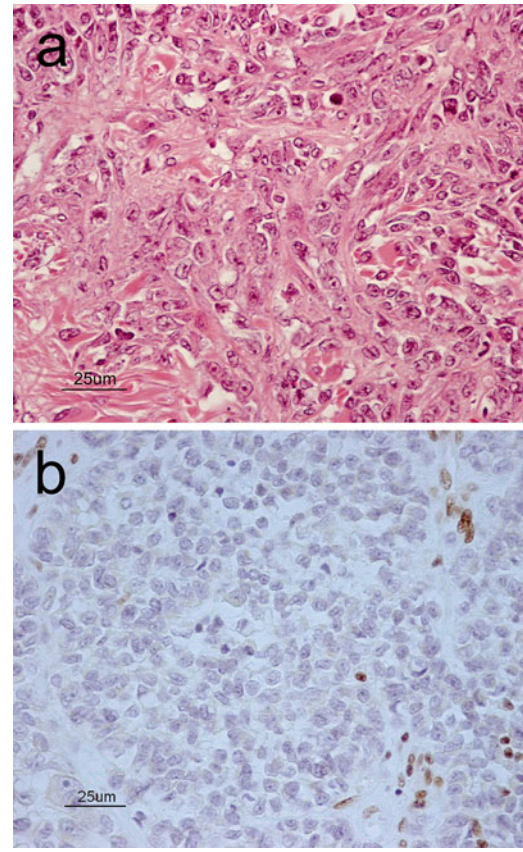

Fig. 6.9 (**a**) ATRT showing sheets of large pleomorphic cells, some of which exhibits globular cytoplasmic eosinophilic material that push the nucleus to the cell edges. Note the prominent nucleoli within vesicular nuclei. H&E, original magnification ×400. (**b**) In ATRT, the tumor cells are negative for INI-1. Original magnification ×400

Ependymomas

Ependymal tumors comprise a group of tumors with variable biological and morphological patterns and include ependymoma, anaplastic ependymoma, myxopapillary ependymoma, and subependymoma. The two most common entities in the pediatric population are ependymoma (WHO grade II) and its anaplastic variant (WHO grade III).

Ependymoma

Ependymoma (WHO grade II) most commonly occurs in the fourth ventricle in children but can be seen throughout the neuraxis. Grossly, ependymomas are usually well-circumscribed, soft

masses with or without cystic changes. They commonly show a solid, fibrillary pattern with the formation of perivascular pseudorosettes (Fig. 6.10a). The latter structures are zones of fibrillary eosinophilic process, free of nuclei, abutting blood vessels. Less commonly, this tumor shows true ependymal rosettes. The cells usually have bland uniform nuclei with granular chromatin and show immunoreactivity with GFAP, vimentin, and S100. Dot-like immunopositivity for EMA is a helpful diagnostic feature but is not always present. Ultrastructural examination is often important in distinguishing the ependymal from astrocytic lineage of the neoplastic cells.

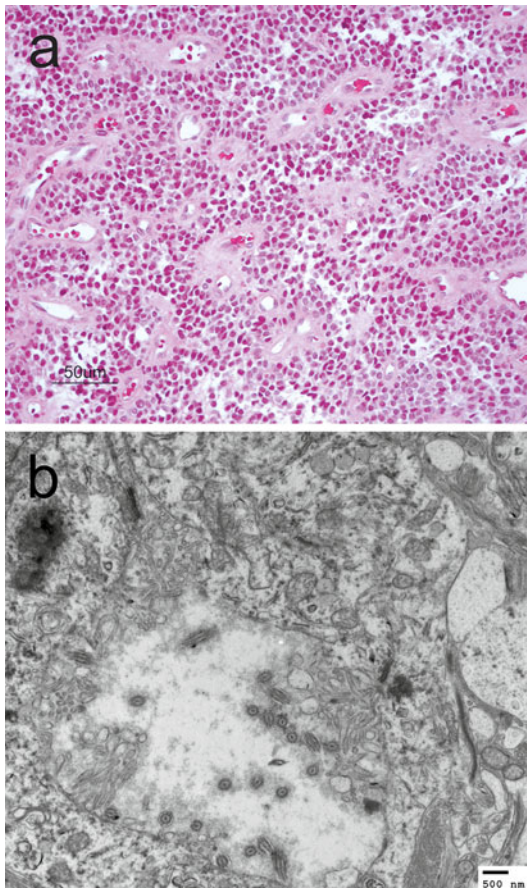

Fig. 6.10 (**a**) Ependymoma showing small bland cells within a fibrillary background. Note the perivascular nuclear-free zones which are characteristic low-power appearance of ependymoma. H&E, original magnification ×200. (**b**) Ultrastructural features of an ependymoma showing microvilli in lumina and long intracellular junctions

The finding of abnormal cilia, intracytoplasmic lumens with microvilli, and long junctional complexes points to an ependymal lineage (Fig. **6.10**b). Morphological variants of ependymoma include cellular, clear cell, papillary, and tanycytic types.

Anaplastic Ependymomas

Anaplastic ependymomas (WHO grade III) are more aggressive appearing tumors that, although grossly well demarcated, tend to have invasive foci and high-grade cytology. Grading however remains controversial. While some authors report prognostic significance of some histological features [24, 25], others have not found a correlation [26, 27]. A more recent study reported that the current histological grading scheme may predict event-free survival, but does not correlate with overall survival [28]. This study emphasized the importance of vascular-endothelial proliferation with endothelial layering (Fig. 6.11a), high mitotic rate, palisading necrosis, and marked hypercellularity with nuclear pleomorphism and/or hyperchromasia as high-grade features. Continued refinement of these criteria for grading ependymal tumors will hopefully allow better prognostication of this group of tumors in the future.

Similar to the molecular subclassification of medulloblastomas, molecular analysis of ependymomas has led to the discovery of subgroups with different clinical outcomes [29]. Gains in chromosome 1q are common in pediatric and

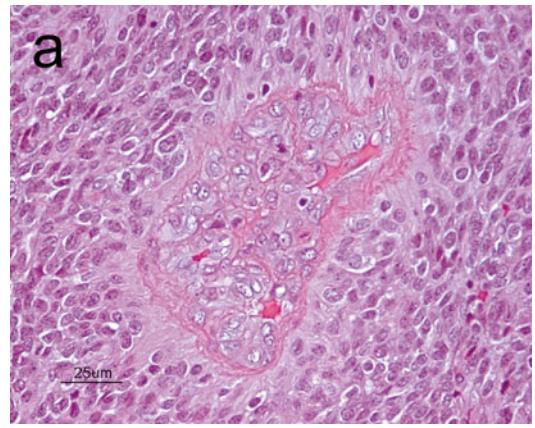

Fig. 6.11 (**a**) Anaplastic ependymoma showing vascular-endothelial proliferation. H&E, original magnification ×400

high-grade (WHO grade III) cases. More specifically, gains of 1q21.1–32.1 are associated with tumor recurrence. Gains of 1q25 represent another independent poor prognostic marker for recurrence-free and overall survival [30].

Choroid Plexus Tumors

Choroid plexus papillomas (CPP, WHO grade I) constitute 2–4 % of pediatric CNS tumors. Choroid plexus carcinomas (CPC, WHO grade III) are five times less common. Both occur in areas where choroid plexus is normally found [31], mainly in the lateral and third ventricles [32] and to a lesser degree in the fourth ventricle (the commonest location in adults).

Choroid Plexus Papilloma

Grossly, CPP forms an enlarged cauliflower-like mass well delineated from the native choroid plexus. Microscopically, it exhibits a normal choroid plexus-like histology with true fibrovascular cores (Fig. 6.12a). The tumor cells typically reside on a basement membrane (Fig. 6.12b), a feature that is helpful in distinguishing it from papillary ependymoma. In contrast to normal choroid plexus papillae, however, the lining epithelial cells show mild nuclear atypia, crowding, pseudostratification, and more complex papillary architecture (Fig. 6.12c). CPP tumor cells can exhibit a wide variety of cellular changes including oncocytic change, mucinous degeneration, and melanization. Immunohistochemical studies show that the lining epithelium is positive for cytokeratin, transthyretin, vimentin, and CK7 and focally for GFAP and EMA. They are usually negative for CK20 [33].

Atypical Choroid Plexus Papilloma

In between choroid plexus papillomas and carcinomas is a relatively new entity termed "atypical CPP." It is essentially similar to CPP but with increased mitotic activity. Two or more mitoses per ten random high-power fields are required for the diagnosis of this entity. In addition, atypical features including increased cellularity, nuclear pleomorphism, blurring of the papillary pattern, and necrosis are commonly seen [34].

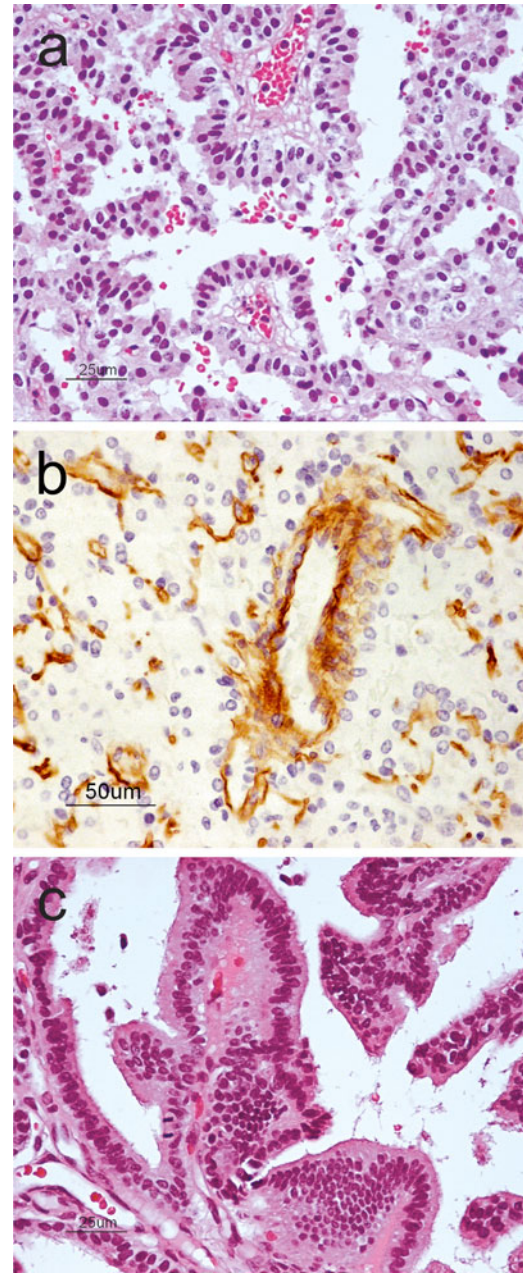

Fig. 6.12 (**a**) Choroid plexus papilloma showing the papillary architecture where the papillae are formed by fibrovascular stroma with overlying columnar epithelium. H&E, original magnification ×400. (**b**) Immunohistochemical staining for laminin highlighting the basement membrane in CPP. Original magnification ×200. (**c**) The epithelial cells lining the papillae are slightly crowded and exhibit minor atypical changes such as mild nuclear pleomorphism, hyperchromasia, and occasional mitoses. H&E, original magnification ×400

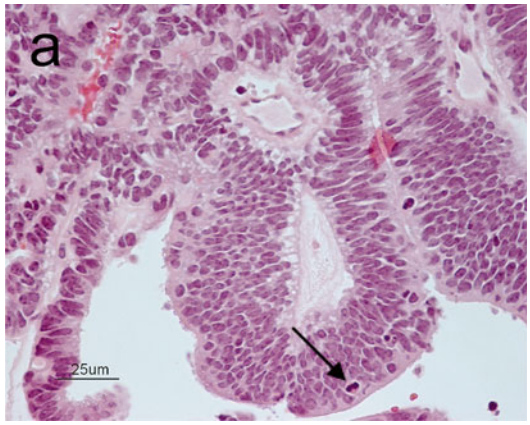

Fig. 6.13 (**a**) Higher-power view of a choroid plexus carcinoma showing nuclear atypia, increased cell density compared with CPP, and frequent mitoses (*arrow*). H&E, original magnification ×400

Choroid Plexus Carcinoma

CPCs usually occur in children under 3 years of age and demonstrate more hemorrhage, necrosis, and invasiveness than CPP. Microscopically, sheets of frankly anaplastic, highly cellular tumor cells with areas of necrosis and frequent mitoses (Fig. 6.13a) are commonly associated with foci that are still reminiscent of a papilloma. Typically, 5–10 mitoses per ten high-power fields are seen. Otherwise, the papillary structures are usually blurred by more solid patterns. The neoplastic cells are usually immunopositive for EMA, cytokeratin, and S100. CPCs can create poorly differentiated patterns that may be confused with embryonal tumors like ATRT, but they retain their immunoreactivity to INI1. Patients with CPC who have absence of TP53 dysfunction have a favorable prognosis and can be successfully treated without radiation therapy [35].

Neuronal and Mixed Neuroglial Tumors

Ganglioglioma

Grossly, gangliogliomas are well-demarcated solid or cystic masses that are often associated with calcifications. This tumor typically exhibits variable degrees of two distinct neoplastic cell populations: glial and neuronal/gangliocytic

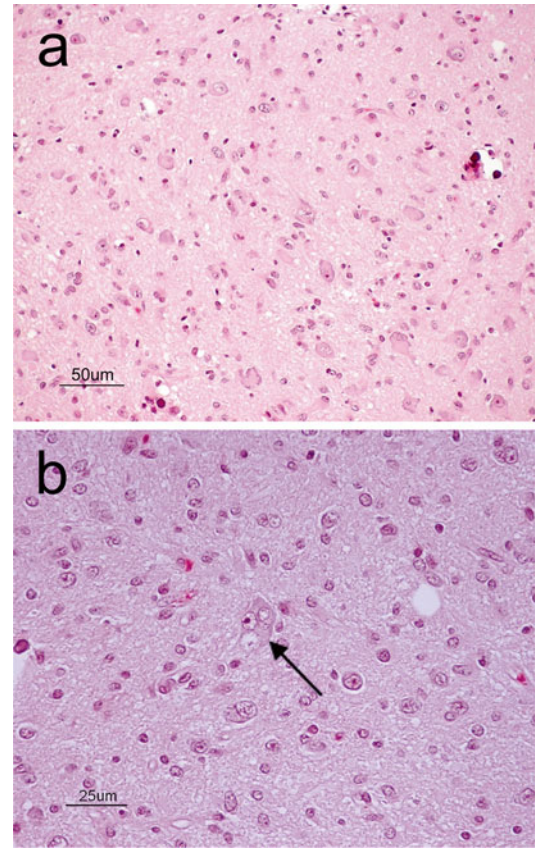

Fig. 6.14 (**a**) Ganglioglioma showing scattered ganglion cells within a rich fibrillary background. H&E, original magnification ×200. (**b**) Ganglion cells are large cells with prominent nucleoli and abundant eosinophilic cytoplasm, some contain basophilic Nissl substance in the periphery of the cytoplasm. Note the binucleation, a feature very rare in normal, non-neoplastic neurons (*arrow*). H&E, original magnification ×400

(Fig. 6.14a). When the tumor is composed solely of neuronal/gangliocytic components, it is referred to as "gangliocytoma, WHO grade I." When a neoplastic glial component is also present, the term ganglioglioma is used and the tumor is graded based upon the glial component; a pilocytic-like glial component is given a WHO grade of I while an anaplastic glial component leads to a WHO grade III designation. Criteria for grade II ganglioglioma have been suggested, but this is not currently an official WHO category [36].

Microscopically, there are ganglion cells with large vesicular nuclei, prominent nucleoli, and abundant cytoplasm where Nissl basophilic mate-

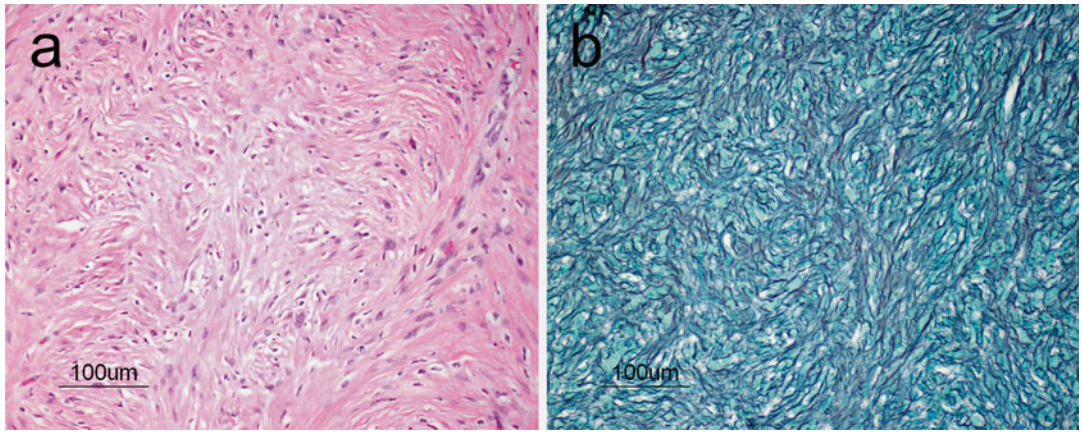

Fig. 6.15 (**a**) Desmoplastic infantile ganglioglioma/astrocytoma showing fascicles of spindled astrocytes within a desmoplastic stroma. H&E, original magnification ×100. (**b**) Reticulin staining highlighting desmoplasia. All pictures, original magnification ×100

rial is present. These neoplastic or atypical ganglion cells show abnormal clustering, pleomorphism, and bi- or multi-nucleation or exhibit large bizarre nuclei (Fig. 6.14b). Eosinophilic granular bodies are typically present and Rosenthal fibers can be seen. Calcifications and perivascular inflammation within a prominent capillary network are common features. Mitotic figures are rare in low-grade gangliogliomas (MIB-1 < 3 %), but are present in the anaplastic variant.

The neuronal/gangliocytic cells are highlighted by immunohistochemistry for NeuN, synaptophysin, or chromogranin. The glial component is highlighted by GFAP. Ultrastructural examination may be used to confirm the presence of both glial and neuronal/gangliocytic components. The former shows glial processes with intracytoplasmic dense fascicles of intermediate filaments, while the latter shows microtubules, electron dense neurosecretory vesicles, and neuritic-type processes.

Anaplastic ganglioglioma can be mistaken for anaplastic astrocytomas that have infiltrated surrounded brain tissue and entrapped nonneoplastic neurons. Recent studies suggest that the BRAFV600E mutation is found more commonly in ganglioglioma than anaplastic astrocytoma (18 % vs 3 %) and thus may be used to differentiate between these two entities in difficult cases [16].

Desmoplastic Infantile Astrocytoma/Ganglioglioma

This is a unique and rare pediatric low-grade glioneuronal tumor (WHO grade I) [37]. It usually affects the supratentorial compartment of children less than 18 months of age. Grossly, it is large, well demarcated, superficial, and typically cystic with involvement of multiple lobes and an attachment to the overlying dura. Desmoplastic infantile astrocytomas are characterized as lesions of low cellularity within a remarkably reticulin-rich desmoplastic stroma containing fascicles, storiform, or whorled patterns of spindled strongly GFAP immunopositive astrocytes (Figs. 6.15a,b). A cortical component without desmoplasia may be observed. This component is usually nodular and often formed by small astrocytes with oval nuclei and eosinophilic cytoplasm. If a population of abnormal binucleated ganglion cells is present, then the tumor is labeled desmoplastic infantile ganglioglioma. The ganglion cells can be difficult to detect without the use of immunohistochemical markers such as synaptophysin and chromogranin. Desmoplastic Infantile Astrocytoma/Ganglioglioma (DIA/G) usually has only rare mitoses and low (<5 %) MIB-1 proliferative index. Although the vast majority of these tumors are benign, some reports suggest that a more aggressive and malignant

behavior is possible when the small cell component shows features of a poorly differentiated embryonal tumor including a high mitotic rate, microvascular proliferation, and necrosis [38].

Dysembryoplastic Neuroepithelial Tumor

Dysembryoplastic Neuroepithelial Tumor (DNETs) are low-grade cortically based tumors (WHO grade I) that have a predilection for the temporal and frontal lobes and often present with a clinical history of chronic seizures. It should not demonstrate mass effect on the surrounding brain tissue. Grossly, it is a well-defined cortical neoplasm that exhibits multinodular, cystic, and/or gelatinous features. Different patterns have been described whose prognostic significance is unclear. These are "typical," "complex," and "nonspecific" [39]. In the simple form, the main constituent is the classic glioneuronal element. This is made up of bland monotonous oligodendroglial-like cells that flank axons, which run perpendicular to the cortical surface. Interspersed are mucinous spaces containing characteristic "floating neurons" with large bland nuclei and prominent nucleoli (Fig. 6.16a). These axons can be highlighted with synaptophysin or neurofilament staining. The oligodendroglial-like cells show positive immunohistochemical reactivity with S100, MAP2, and Olig2. In addition, a subpopulation of cells may be positive for neuronal markers such as NeuN or synaptophysin. GFAP stains the glial components.

Complex is a term that is used when the tumor has adjacent glial nodules in addition to the specific glioneuronal element. More diffuse glial components can also be seen. These often mimic a low-grade glioma but may also show some atypical features like nuclear atypia, occasional mitoses, microvascular-like proliferation, or ischemic necrosis [2]. Lastly, a controversial "nonspecific" variant has been proposed that lacks the classic histological features. It comprises mainly glial elements and would otherwise be characterized as a "low-grade glioma." Diagnosis as a nonspecific DNET is thus made based on clinicopathological correlation of a child with a radiological stable, well-circumscribed lesion with an associated history of chronic seizures.

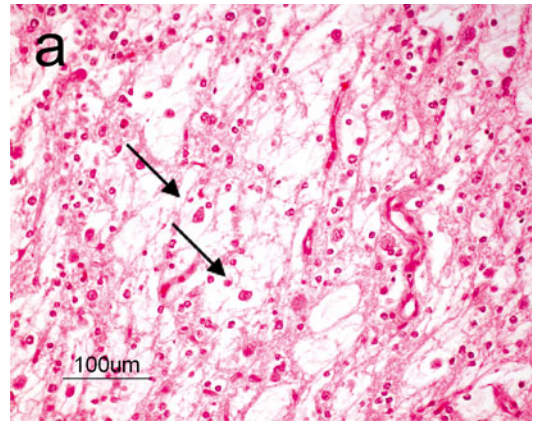

Fig. 6.16 (**a**) DNET showing bundles of axons lined with oligodendroglial cells and microcystic changes in a myxoid background with floating neurons (*arrows*). H&E, original magnification ×100

Non-neuroepithelial Tumors

Craniopharyngioma

Craniopharyngiomas (WHO grade I) usually affect the suprasellar region where they are thought to arise from Rathke's pouch remnants. It has two variants, adamantinomatous and papillary. The former is most common in the pediatric population where it accounts for 5–10 % of intracranial tumors making it the most common form of non-neuroepithelial neoplasm [40]. It usually has solid, firm, and cystic components with contents that resemble motor oil due to the nature of the mixture of blood, proteins, and cholesterol crystals. The tumor exhibits poor circumscription and has sheets, nests, and trabeculae of epithelial cell sheets in a fibrous stroma. The epithelium demonstrates a characteristic morphology where the peripheral cells show nuclear palisading while the central cells form a loose "stellate reticulum" (Fig. 6.17a). Also present are characteristic areas of "wet keratin" that frequently calcify (Fig. 6.17b). The presence of one of the latter two features (the stellate reticulum or the wet keratin) is diagnostic of craniopharyngioma [1]. In addition, cystic changes, xanthogranulomatous reaction, and cholesterol clefts are frequent findings in a craniopharyngioma. Variable degrees of necrosis can be seen and do not indicate a malig-

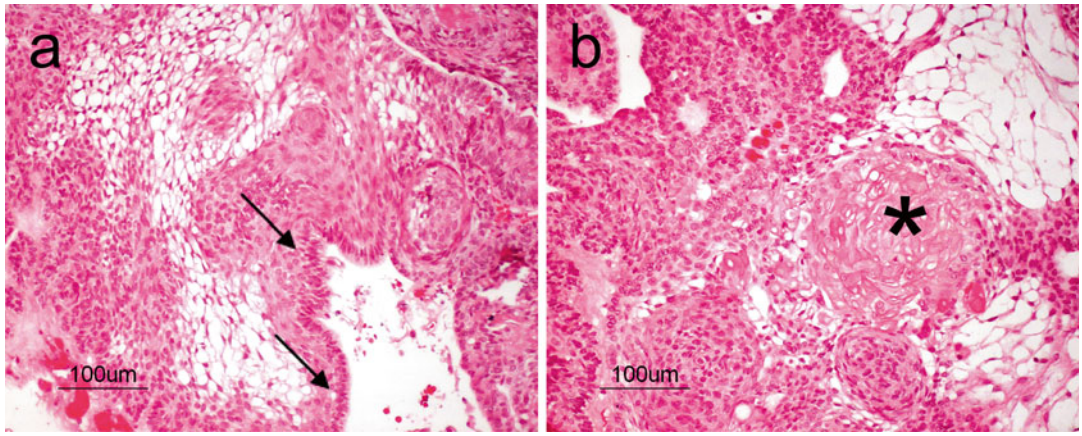

Fig. 6.17 (**a**) Craniopharyngioma showing palisaded epithelial cells, the loose stellate reticulum (*arrows*). H&E, original magnification ×100. (**b**) Characteristic wet keratin (*asterisk*) of craniopharyngioma. H&E, original magnification ×100

nant nature. Craniopharyngioma can be associated with piloid gliosis in the surrounding brain tissue where Rosenthal fibers are prominent. The latter can be confused with low-grade astrocytic neoplasms, particularly on frozen section.

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